Update on Progress in HIV Pre-Exposure Prophylaxis

Challenges and opportunities on how to address women in PreP trials

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HELPING THE PHARMACEUTICAL INDUSTRY
SUPPORT A GLOBAL RESEARCH AGENDA FOR WOMEN
IAS INDUSTRY LIASON FORUM

XVII International AIDS Conference (AIDS 2008)
Hall 10, AIDS2008, Mexico City
Monday 4 August 2008
PrEP Goes Back to Basics

- HIV Infection is the Cause of AIDS
  - Not Sex, Not Drugs
  - Antiretroviral Agents Target HIV Directly
- People Like Sex
  - For Pleasure, Intimacy, Company, Livelihood, and Pregnancy....
  - Prevention is less used if it alters sex
    - Abstinence Programs, Condoms, Diaphragm
    - Microbicides? Male circumcision?
- Condom use, the main barrier method, is mainly male-controlled
Why Chemoprophylaxis?

- Anti-HIV Drugs
  - Inhibit HIV directly
  - Are already formulated and mass produced
  - Prevent mother to child transmission
- A pill is at least as female-controlled as a topical microbicide
- Chemoprophylaxis is a proven concept
  - EG: Malaria, TB pneumonia, meningitis
Why Pre-exposure?

- Pre-exposure dosing increases efficacy
  - SHIV exposed nonhuman primates (Garcia Lerma 2008)
- People have difficulty recognizing exposure
  - Denial (Schechter J AIDS 2004)
  - Substance use
  - Imperfect communication with partners
- For those at highest risk
  - Pre- and post-exposure periods overlap
Rationale for Pre Exposure Prophylaxis

- Used Daily
- Concept is proven for prevention of
  - Malaria (80 to 90% effective)
  - Tuberculosis Pneumonia (90% effective)
  - Unwanted Pregnancy (99% effective)
- Drug Is Initiated Before Large Infections Occur
- Can Be Initiated By Women
- Coordination with Risk Behavior Is Not Needed
- Requires Identification of High Risk Groups
  - But Not Specific High-Risk Acts
PrEP: The Key Points

- PrEP is a potential new HIV prevention intervention that could have an important impact on HIV prevention globally

- Only tenofovir (TDF) and a combination of TDF and emtricitabine (FTC) are currently being tested in clinical trials for use as PrEP

- Although exists enough confidence that either TDF or TDF/FTC would work for PrEP, this should not preclude the evaluation of other antiretrovirals for PrEP
## Ongoing and Planned PrEP Trials as of August 2008

<table>
<thead>
<tr>
<th>Location</th>
<th>Sponsor/Funder</th>
<th>Population (mode of exposure)</th>
<th>Intervention arms</th>
<th>PrEP strategy(ies) being tested</th>
<th>Status / Expected completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>CDC</td>
<td>400 gay men and other men who have sex with men (penile/rectal)</td>
<td>1</td>
<td>TDF</td>
<td>Fully enrolled – Ongoing / 2009</td>
</tr>
<tr>
<td>Thailand</td>
<td>CDC</td>
<td>2,400 injecting drug users (parenteral)</td>
<td>1</td>
<td>TDF</td>
<td>Enrolling / 2009</td>
</tr>
<tr>
<td>Botswana</td>
<td>CDC</td>
<td>1,200 heterosexual men and women penile and vaginal</td>
<td>1</td>
<td>TDF/FTC (switched from TDF Q1 2007)</td>
<td>Enrolling / 2010</td>
</tr>
<tr>
<td>Brazil, Ecuador, Peru, US, additional sites TBD (PrEx Study)</td>
<td>NIH, BMGF</td>
<td>3,000 gay men and other men who have sex with men (penile/rectal)</td>
<td>1</td>
<td>TDF/FTC</td>
<td>Enrolling / 2010</td>
</tr>
<tr>
<td>Kenya, Uganda (Partners PrEP Study)</td>
<td>BMGF</td>
<td>3,900 serodiscordant heterosexual couples (penile and vaginal)</td>
<td>2</td>
<td>TDF; TDF/FTC</td>
<td>Enrolling / 2012</td>
</tr>
<tr>
<td>Southern Africa; specific sites TBD (VOICE Study)</td>
<td>MTN, NIH</td>
<td>4,200 sexually active women (vaginal)</td>
<td>3</td>
<td>TDF; TDF/FTC; TDF gel</td>
<td>Planning / 2012 Anticipated start Q1/2009</td>
</tr>
</tbody>
</table>


Anticipating the Results of PrEP Trials. AIDS Vaccine Advocacy Coalition. August 2008
The iPrEx Study
Safety, Efficacy, Behavior, and Biology
Gladstone Institute of Virology and Immunology
iPrEx Study Successfully Enrolling

<table>
<thead>
<tr>
<th>Enrollment Status (Started Operations)</th>
<th>IMPACTA, Lima (June 2007)</th>
<th>INMENSA, Lima (July 2007)</th>
<th>ACSA, Iquitos (July 2007)</th>
<th>EQUIDAD, Guayaquil (November 2007)</th>
<th>SFDPH, San Francisco (June 2008)</th>
<th>FENWAY, Boston (June 2008)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>853</td>
<td>626</td>
<td>447</td>
<td>180</td>
<td>15</td>
<td>8</td>
<td>2129</td>
</tr>
<tr>
<td>Eligible</td>
<td>494</td>
<td>448</td>
<td>336</td>
<td>114</td>
<td>12</td>
<td>6</td>
<td>1410</td>
</tr>
<tr>
<td>Ineligible</td>
<td>359</td>
<td>178</td>
<td>111</td>
<td>66</td>
<td>3</td>
<td>2</td>
<td>719</td>
</tr>
<tr>
<td>Enrolled</td>
<td>300</td>
<td>299</td>
<td>300</td>
<td>84</td>
<td>10</td>
<td>6</td>
<td>999</td>
</tr>
<tr>
<td>Eligible but no enrolled</td>
<td>194</td>
<td>149</td>
<td>36</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>411</td>
</tr>
</tbody>
</table>

Screening: Enrollment ratio: 2.13

iPrEx Study: Successfully Enrolling

Enrollment Trend
All Open Sites, as of July 26, 2008

July 1 - July 7
July 15 - July 21
July 29 - Aug 4
Aug 12 - Aug 18
Aug 26 - Sep 1
Sep 9 - Sep 15
Sep 23 - Sep 29
Oct 7 - Oct 13
Oct 21 - Oct 27
Nov 4 - Nov 10
Nov 18 - Nov 24
Dec 2 - Dec 8
Dec 16 - Dec 22
Dec 30 - Jan 5
Jan 13 - Jan 19
Jan 27 - Feb 2
Feb 10 - Feb 16
Feb 24 - Mar 1
Mar 9 - Mar 15
Mar 23 - Mar 29
Apr 6 - Apr 12
Apr 20 - Apr 26
May 4 - May 10
May 18 - May 24
Jun 1 - Jun 7
Jun 15 - Jun 21
Jun 29 - Jul 5
Jul 13 - Jul 19
PrEP and Women

- Low-risk persons can become high-risk persons, and vice versa
- HIV transmission can occur:
  - In sexual contacts between female sex workers and their clients
  - Through marriage-like relationships
  - “Leakage” from infected individuals reflecting all non-paid casual sex
- HIV transmission through marriage and “leakage” only occurs in low risk groups
PrEP and Women: What Would Affect PrEP Efficacy and/or Safety?

- Differences in body composition and size
- Differences in pharmacokinetics
- Differences in woman-specific concomitant medication use
  - E.g.: Contraception
- Differences in modes of exposure
- Differences in transmission rates
Conducted between June 2004 and March 2006
West Africa
Daily dose of 300 mg oral Tenofovir DF vs. placebo
All participants received testing, condoms, and counseling.
Safety evaluated in N=936 including 428 person years
<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of partners (30 days)</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Number of new partners (30 days)</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Number of sex acts (7 days)</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Condom use (last act)</td>
<td>52%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Peterson, *Plos Clinical Trials*, 2007
Findings From the West African PrEP Study

Safety in seronegatives confirmed
- No increase in grade 1 renal abnormalities
- No grade 2 or greater renal toxicity
- No flares among 23 known to be HBsAg+

A trend toward efficacy
- 8 seroconversions (2 TDF: 6 Placebo; P=0.34)
- 2 seroconversions after 1 and 2 months of TDF
  - No specimens to Rule Out Pre-PREP infection
  - No *bona fide* case of PREP failure yet documented

Peterson, *Plos Clinical Trials*, 2007
Pre-exposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child

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¹Division of Infectious Diseases and ²Social Services, Cantonal Hospital St. Gallen,

# License to Love

## Counselling of HIV Discordant Couples

1. Discordant couples: Male HIV+/Female HIV-
2. Information to both partners about transmission risks
3. Rule out asymptomatic STDs
4. Maintain fully suppressive HAART
5. Timing of unprotected intercourse
   - 36 h after LH-peak (urine)
6. HIV-Pre-Exposure Prophylaxis (TDF)
   - 2 doses 0 and 24 h after LH-peak

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License to Love

Pregnancy-Rates in First 22 Couples

Potential Impact of Antiretroviral Chemoprophylaxis on HIV-1 Transmission in Resource-Limited Settings

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1 Division of Infectious Diseases, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, 2Department of Infectious Disease Epidemiology, Imperial College, Faculty of Medicine, University of London, London, United Kingdom

Table 5. Potential Impact of PrEP Introduced in 2007 on HIV-1 Infections in Southern Sub-Saharan Africa⁴

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>Baseline Adult HIV Prevalence %</th>
<th>Baseline Adult HIV Incidence %</th>
<th>Baseline Adult Population people</th>
<th>Population Growth Rate %</th>
<th>Cumulative New HIV Infections Averted after 10 Years</th>
<th>Optimistic Scenario &amp; Targeted by Sexual Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No Disinhibition</td>
</tr>
<tr>
<td>Lesotho</td>
<td>23.2</td>
<td>4.8</td>
<td>865 000</td>
<td>0.1</td>
<td>92 710</td>
<td>100% Disinhibition</td>
</tr>
<tr>
<td>Botswana</td>
<td>24.1</td>
<td>6.7</td>
<td>909 000</td>
<td>0.1</td>
<td>132 870</td>
<td>81 608</td>
</tr>
<tr>
<td>Zambia</td>
<td>17.0</td>
<td>2.6</td>
<td>5 281 000</td>
<td>1.7</td>
<td>361 132</td>
<td>221 803</td>
</tr>
<tr>
<td>South Africa</td>
<td>18.8</td>
<td>2.4</td>
<td>25 204 000</td>
<td>0.8</td>
<td>1 477 691</td>
<td>907 581</td>
</tr>
<tr>
<td>Southern Sub-Saharan Africa⁵</td>
<td>19.6†</td>
<td>2.4</td>
<td>54 836 000</td>
<td></td>
<td>2.713 746–3 166 037</td>
<td>1 666 752–1 944 544</td>
</tr>
</tbody>
</table>

¹These are conservative projections based on estimates of the size of adult population [47,71] and assuming constant incidence [73–75,89], prevalence [47] and growth rate [47].
²For southern sub-Saharan Africa overall, projections are based on the UNAIDS/WHO statement that the total number of infections in this region were 1.1 million for three consecutive years including 2005 [75]. With this estimate as a constant, low projection assumes 86% of these infections occur in adults, while the high projection assumes the full estimate.
³Excludes Angola, Madagascar, Mauritius and Seychelles.
⁴Refers to median country-prevalence.
⁵doi:10.1371/journal.pone.0000875.0005

Abbas, Plos
The Impact of Pre-Exposure Prophylaxis (PrEP) on HIV Epidemics in Africa and India: A Simulation Study


Figure 1. Effect of different PrEP scenarios and condom use on HIV prevalence. A: Botswana, B: Nyanza province, Kenya. ‘PrEP low’ means 25% coverage and 50% effectiveness; ‘PrEP high’ means 75% coverage and 90% effectiveness; ‘Only CSW’ means target group is sex workers; ‘CSW&client’ means target group is sex workers and clients. doi:10.1371/journal.pone.0002077.g001
PrEP in Women: Recommendations

- Women are included in the PrEP research agenda
  - PrEP efficacy study results are expected in MSM and/or IDU before than in female populations
    - Careful interpretation and extrapolation to women
- Intervening women in settings where HIV is mainly “heterosexually” transmitted would have an important impact in the epidemic
- Social stigma/discrimination and access to PrEP are barriers to be addressed once PrEP programs are implemented
  - Coupling PrEP to other female-targeted intervention (e.g.: contraception) would have a higher impact in preventing HIV